A1 CONT.

or crystalline adduct of a member selected from the group consisting of alpha1-antitrypsin, secretory leucocyte protease inhibitor and alpha2-macroglobulin so as to inhibit collagenase and tumor necrosis factor alpha activity.--

Remarks

With regard to applicants' claim for priority as a continuation-in-part of U.S. App. No. 09/885,654, it is noted that on page 3 last paragraph, there is mentioned autoimmune disease which the present claims are directed. Also, a part of the disclosure is found in the present application.

With regard to the election, applicants admit that all of the species are obvious over each other. Also the claims have been limited to the treatment of an autoimmune disease which is rheumatoid arthritis.

The Rejection Under 35 USC 103(a)

Reconsideration is respectfully requested of the rejection of the claims as now presented as being unpatentable over WO 00/51623 in view of U.S. Patent Np. 4496689 and WO 99/55310.

The present claims relate to the treatment of the autoimmune disease rheumatoid arthritis. As noted from the Merck Manual, which is submitted, rheumatoid arthritis is present in two different forms. One form is the type characterized by inflammation and the degrannulation of mast cells. The other type of rheumatoid arthritis is autoimmune. In autoimmune arthritis, the inflammation is gone and there are autoantibodies circulating throughout the body as well as compliment components and Fc receptors which participate in the pathogenesis of erosive arthritis. It is known that members of the complement network (the alternative pathway and C5a), Fc receptors (FcγRIII)and

cytokines (interleukin 1), TNF-α as well as neutrophiles have essential roles. The antibodies cause the release of TNF-α. The circulation causes an attack on other joints in the body and not only the joint which is initially inflammed. It is known that alpha1-antitrypsin binds with antibodies, TNF-α, the Fc receptor and complements. However, alpha1-antitrypsin when administered orally circulates through the body and binds with the factors causing the arthritis without mast cell inflammation. Alpha1-antitrypsin binds with each of Fc receptors, TNF-α and complements. Alpha2-macroglobulin comprises half the structure of the alpha1-antitrypsin molecule and secretory leucocyte protease inhibitor contains similar binding site.

WO '623 teaches a theory that has for years been proven to be wrong. Alpha1-antitrypsin cannot be administered orally and survive the bile acids in the gut. This was proven in emphysema and cystic fibrosis studies. It is for this reason that Mitra '689 at column 9 lines 8-15 teaches intravenous use for pulmonary emphysema therapy. The object of Mitra was to utilize a pro drug as replacement therapy in a disease related to alpha1-antitrypsin deficiency. Mitra supports applicants' position that there is a distinction between natural alpha1-antitrypsin and the protein which is conjugated. In 1989, Hubbard et al of the University of Pennsylvania published that alpha1-antitrypsin had no pharmaceutical activity but was only useful as replacement therapy.

Lezdey '917 relates to alpha1-antichymotrypsin. It is stated at column 3 lines 1-3 that alpha1-antitrypsin is for inflammation. In addition, applicants have a pro drug having a different physical and chemical properties.

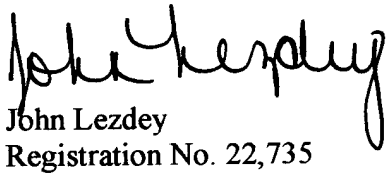
WO '310 does not treat rheumatoid arthritis. Moreover, the combination of WO '310 and US '689 would not lead one in the art to a treatment of an autoimmune disease which is not related to mast cells.

It is recognized that corticosteroids are useful in treating inflammatory diseases. There is a Lezdey patent related to the combination of alpha1-antitrypsin and a steroid for pulmonary inflammation. In the present case, the steroid is primarily because of the Interleukin I and not for inflammation.

In recapitulation, the prior art does not teach or suggest the treatment of a non-inflammatory disease, namely, rheumatoid arthritis when it becomes a collagen related disease in which mast cells are not involved. Furthermore, the drugs utilized are pro drugs which distinguish over native proteins. It is because the disease is distinguished from mast cell diseases that alpha2-macroglobulin and secretory leucocyte protease inhibitor are useful. Secretory leucocyte protease inhibitor and alpha2-macroglobulin do not prevent mast cells from degrannulating. Both drugs bind with complements and IL-1.

Reconsideration and favorable action are earnestly solicited.

Respectfully submitted,



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